REMARKS

Claims 1-6, 9, 11-15, 17-20, and 22-26 are pending in the instant application. By this amendment, Claims 1, 2, 4, 5, 9, and 11-15 have been amended and Claims 23-26 have been cancelled, without prejudice to applicants' rights to pursue the cancelled subject matter in this or related applications.

In particular, Claims 4 and 9 have been amended to correct minor clerical errors. Claim 2 has been amended to more particularly point out and distinctly claim the invention. In particular, Claim 2 has been amended to make it clear that the neurodegenerative condition of Claim 1 is a neurodegenerative disease. Claim 5 has been amended to add the limitation of rectal administration, support for which is found in the specification, for example at page 23, lines 23-25. In addition, Claim 11 has been amended and reformulated as an independent claim, by adding the preamble language, "A method for protection of neuronal tissue from injury or tissue damage." Support for this amendment is found, for example, at page 18, line 33 to page 19, line 18, especially page 19, lines 16-18. Claim 12 has been amended to depend on Claim 11. Support for this amendment is found, for example, at Section 8 (Example 30), especially page 32, lines 9-13; and Section 13 (Example 8), especially page 35, lines 16-20 and Figure 8B. Support for Claim 13, amended to depend on Claim 11, is found at Section 5.2.2, especially page 14, lines 10-14 and lines 24-26. Support for Claim 14, amended to depend on Claim 11, is found at page 18, line 33 to page 19, line 18, especially page 19, lines 16-18.

Therefore, no new matter has been added. Claims 1-6, 9, 11-15, 17-20, and 22 will be pending upon entry of the instant amendment.

A. INTERVIEW SUMMARY

At the outset, applicants thank Primary Examiner Regina DeBerry, and Supervisory Examiner Marianne Allen for the courtesies extended during the interview of April 16, 2007 at the United States Patent and Trademark Office ("the Interview"). Present at the Interview were Drs. Anthony Cerami and Michael Brines, two of the inventors of the instant application, Frederick J. Hamble, Esq., of Warren Pharmaceuticals, Inc., Mary Catherine DiNunzio of Lundbeck Pharmaceuticals, and applicants' representatives Eileen E. Falvey and Laura A. Coruzzi of Jones Day.

During the Interview, the outstanding rejections made in the Office Action dated February 1, 2007 (the "Office Action") were discussed. In particular, the allowability of the limitation "administering peripherally" in all claims and deletion of the limitation "neurodegenerative condition" in Claims 12 and 24 were discussed. In addition to the outstanding rejections, the Examiners requested further consideration of the scope of the enablement of the limitation "neurodegenerative condition." The amendments above and the following remarks reflect suggestions made by the Examiners and the content of the discussion during that Interview.

B. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SCOPE OF ENABLEMENT, SHOULD BE WITHDRAWN

Claims 1-6, 9, 11-15, 17-20, and 22-26 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement in the specification commensurate in scope with the claims.

1. The Legal Standard

The test for enablement is whether one reasonably skilled in the pertinent art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v.* Telectronics *Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). Under 35 U.S.C. § 112, it is not fatal that a certain amount of experimentation may be required to adapt the invention to a specific purpose, provided the experimentation is routine. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In *Wands*, the Federal Circuit held that undue experimentation is determined by a standard of reasonableness which can be assessed by examining eight factors: (1) quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *Id.*

With regard to the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244, 68 USPQ2d 1280, 1287 (Fed. Cir. 2003); *In re Moore*, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971). See also *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339, 65 USPQ2d 1452, 1455 (Fed. Cir. 2003)

(alleged "pioneer status" of invention irrelevant to enablement determination). The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of the enablement involves two stages of inquiry. The first is to determine how broad the claim is with respect to the disclosure. The second inquiry is to determine if one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation. M.P.E.P. § 2164.08.

2. <u>The Full Scope of the Limitation "Peripheral Administration" is Enabled</u>

The Examiner states at page 5, first full paragraph, that Claims 4, 5, 18 and 19 are not enabled because "the specification and the art of record fail to teach that EPO can cross the blood/brain in routes besides intravenously and intracranially." Applicants respectfully disagree, for the reasons set forth below.

As a result of the inventors' discovery that erythropoietin is transported across the blood brain barrier, peripheral administration of erythropoietin for protection of excitable tissue is disclosed in the specification, see, *e.g.*, application at Section 5.4.3, pp. 27-28, especially, p. 27, *ll.* 8 to p. 22. Erythropoietin can be peripherally administered through oral and parenteral routes (p. 21, *l.* 31-p. 22, *l.* 4; p. 23, *ll.* 21-27; p. 27, *l.* 7 to p. 28, *l.* 26).

The specification discloses that EPO can cross the blood-brain barrier and protect neural tissue from injury and damage. For instance, the specification provides an example of peripherally administered EPO used to protect mice from neurodegeneration and neuronal injury in the kainate model, a commonly-accepted mouse model for neurodegeneration and neural injury (Example 3, pages 31, line 3, to page 32, line 13). The example demonstrates that intraperitoneally administered EPO was able to cross the blood-brain barrier to protect mice from the neurotoxin kainate. The specification also provides working examples of peripherally administered EPO for enhancing learning and cognitive function (Examples 1 and 2, page 28, *l.*, 29, to page 31, *l.* 2). These examples demonstrate the ability of peripherally administered EPO to cross the blood-brain barrier to the brain, where it exerts a neuroprotective effect. Thus, once in the blood stream, EPO can cross the blood-brain barrier and protect neural tissue from injury and damage.

The use of intravenous and intracranial routes of administration are proof of the principle that any method known in the art for administering a pharmaceutical compound such as erythropoietin into the blood stream, including intra-arterial, intramuscular, submucosal, intraperitoneal, subcutaneous administration, can be used by one of skill in the

art to administer EPO for the purposes of the instant invention. Such methods for administration of compounds are well within the knowledge of the skilled artisan, and introducing EPO into the blood stream by any of these methods would not require undue experimentation.

Thus, given the extensive direction provided in the specification, the examples provided in the specification of intravenous and intracranial administration, the amount of experimentation required to try to administer EPO into the blood stream using other well-known modes of administration, and the relatively high skill and predictability in the practice of administering peptide compounds such as EPO into the blood stream, applicants submit that no undue experimentation would be required of the skilled artisan to make and use the claimed invention across the entire scope of the claims.

3. The Full Scope of the Limitation "Neurodegenerative Condition" is Enabled

In this Section, as requested by the Examiners at the Interview, applicants address the issue of scope of enablement of the limitation "neurodegenerative condition." Preliminarily, it should be noted that this issue has been previously addressed in this case (see pages 4-5 of Amendment under 37 C.F.R. § 1.111 dated February 26, 2003, and accompanying Declaration of Michael L. Brines). In fact, at page 3 of the Office Action the Examiner indicated that the scope of this limitation is enabled, at least with respect to certain modes of administration. Thus, although there are presently no outstanding rejections with respect to the scope of enablement of the limitation "neurodegenerative condition," in order to address concerns expressed by the Examiners at the Interview, this issue is further discussed below.

The instant application provides extensive disclosure on how EPO can be used to protect neural tissue and treat neural damage resulting from such hypoxic conditions, and thereby protect against and treat a broad assortment of neurodegenerative conditions. Neurodegenerative conditions, as used in the specification, include a variety of conditions that result from reduced oxygenation, or "hypoxic conditions" of neuronal tissue, and the use of erythropoietin for protection of excitable tissue in mammals having a neurodegenerative condition is taught throughout the specification (see, e.g., Section 5.3, page 18, line 31 to page 21, line 27). Such neurodegenerative conditions may arise from neurodegenerative disease or injury to neuronal tissue, causing hypoxic conditions, resulting in stress, damage, and finally, neuronal cell death (see specification at page 19, lines 7 to 9).

The specification provides working examples demonstrating the use of EPO for protection of neural tissue in mammals having neurodegenerative conditions. A working example using the kainate model is disclosed in Example 3, page 31, line 3 to page 32, line 13. In this example, mice were peripherally administered recombinant human erythropoietin (PROCRIT, 100 U per dose, intraperitoneally) prior to receiving the excitatory neurotoxin kainate. The example demonstrates that EPO can protect mice from acute injury and resulting neural damage caused by kainate.

The kainate model is a well-known, art-accepted model of mammalian neurodegenerative conditions, including neurodegenerative disorders and diseases and neuronal injury. (*See* Wang *et al.*, 2005, Molecular Neurobiology, 31: 3-16 (Cited Reference FG)). Kainate, or kainic acid, is an analog of the excitatory neurotransmitter glutamate, which, as discussed below, is the major contributor to pathological cell death in the central nervous system (CNS). *Id., see* also Segura-Aguilar *et al.*, 2004, *Neurotoxicity Research* 6: 615-630 (Cited Reference FC), at pages 619-620; Trist, 2000, *Pharmaceutica Acta Helvetiae* 74: 221-229 (Cited Reference FF), see Abstract on page 221; Salinska *et al.*, 2005, *Folia Neuropatholica* 43(4): 322-339 (Cited Reference FA) at pages 322-323. In this model, excessive stimulation of glutamate receptors by an increased concentration of their agonist, the glutamate analog kainate, results in oxidative stress, necrosis, apoptosis, and ultimately neurodegeneration and neuronal cell death.

Common mechanisms underlie the wide variety of known neurodegenerative conditions, and glutamate excitotoxicity is accepted to be the most important underlying mechanism (*see* Wang *et al.*, page 3). Glutamate is the major excitatory neurotransmitter in the mammalian CNS, but an excessive concentration of glutamate results in excessive neuronal excitation and oxidative stress. The resultant hypoxic conditions cause necrosis, apoptosis, and ultimately neurodegeneration and neuronal cell death. This progression of neuropathology is common to most, if not all, neurodegenerative conditions.

In fact, changes in glutamate transmission through its receptors is known to be associated with a number of CNS neurodegenerative conditions, including chronic neurodegenerative diseases like Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease, chronic pain, depression, drug dependency, epilepsy, Parkinson's disease, AIDS dementia, epilepsy, and schizophrenia (see Salinska *et al.*, pages 330-332). Indeed, the pattern of neuronal loss in the striatum of Huntington's Disease is similar to that obtained after excitotoxic lesions in animals (see Salinska *et al.*, page 331), and the similarity of the

pattern of neuronal loss in the spinal cord of Amyotrophic Lateral Sclerosis (ALS) patients and that obtained after excitotoxic lesions induced with kainate in animals (Salinska *et al.*, page 331) indicates that the neurodegeneration caused by glutamate excitotoxicity exemplifies the oxidative stress, necrosis, apoptosis, and neurodegeneration observed associated with a wide range of neurodegenerative conditions (see Salinska *et al.*, pages 330-331).

Because the kainate model is widely accepted in the art to apply to neural damage caused by a broad variety of neurodegenerative conditions, the experimental proof provided in Example 3 that peripherally administered EPO protects neural tissue from excitotoxic damage in the kainate model is applicable to a broad array of neurodegenerative conditions. Thus, given the extensive guidance provided by the specification, including the working example using an art-accepted model of neurodegenerative conditions, and the high level of skill and predictability of the art, Applicants submit that the skilled artisan would be able to make and use the claimed invention across the entire scope of the claim limitation "neurodegenerative condition" without undue experimentation.

4. <u>Claims 11-14 and 23-26 are Described and Enabled by the Specification</u>

The Examiner states at pages 4-5 of the Office Action that the specification is not enabling for a method for protection of a mammal from a medical or surgical procedure, wherein said mammal is either suffering from a neurodegenerative condition, as recited in Claims 11-14, or has a mechanical trauma, diabetic neuropathy or amyotrophic lateral sclerosis, as recited in Claims 23-26.

In addition, the Examiner states at pages 6-8 of the Office Action that Claims 11-14 and 23-26 fail to comply with the written description requirement and are new matter. The Examiner contends that the specification as originally filed does not provide support for methods of protecting excitable tissue in a mammal who already has a neurodegenerative disease or mechanical trauma, diabetic neuropathy, or amyotrophic lateral sclerosis by EPO administered prior to a medical or surgical procedure.

In response, Claims 11-14 have been amended and Claims 23-26 have been cancelled. Claim 11 has been amended and reformulated as an independent claim, by adding the preamble language, "A method for protection of neuronal tissue from injury or tissue damage." This language is supported and enabled in the specification at page 18, line 33 to page 19, line 18, particularly page 19, lines 16-18. Claim 12 has been amended to depend on

Claim 11, and is supported and enabled by the specification at page. 32, lines 9-13; and page 35, lines 16-20. Claim 13 has been amended to depend on amended Claim 11, and is supported and enabled at page 14, lines 10-14 and lines. 24-26 of the specification. Claim 14, amended to depend on amended Claim 11, is supported and enabled at page 18, line 33 to page 19, line 18, especially page 19, lines 16-18 of the specification.

As such, the rejection of Claims 11-14 and 23-26 for lack of written description and enablement should be withdrawn.

In view of the foregoing amendments and arguments, applicants submit that the rejections for scope of enablement and written description (new matter) under 35 U.S.C. §112, first paragraph, have been overcome and/or obviated and should be withdrawn.

C. THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, FOR INDEFINITENESS SHOULD BE WITHDRAWN

Finally, the Examiner states at page 10 of the Office Action that Claims 1, 12, 15, and 24 are indefinite because the use of the language "does not increase the hematocrit in said mammal" in Claims 1 and 15, and the language "an effective non-toxic amount" in Claims 12 and 24, is not clear. Applicants submit that this rejection is obviated by the present amendment, for the reasons discussed below.

The Examiner's concern appears to be a lack of clarity regarding the difference in scope between the term "a non-toxic amount of EPO" and the term "an amount of EPO that does not increase the hematocrit." Applicants believe that any issue of lack of clarity resulting from the use of both terms is moot in view of the present amendment. In particular, by this amendment, Claim 12 has been amended to depend on Claim 11, and Claim 24 has been cancelled. As amended, Claims 1, 11, and 15 contain the expression "does not result in a toxic increase in hemoglobin concentration or hematocrit in said mammal," but do not contain the term "a non-toxic amount of EPO." As such, Applicants believe that Claims 1, 12, and 15 are clear and definite for the reasons set forth below.

The amended phrase "without a toxic increase in hemoglobin concentration or hematocrit" in claims 1, 11, and 15 is clear and unambiguous, requiring that the amount of erythropoietin administered is effective to exert a neuroprotective effect without an increase in hemoglobin concentration or hematocrit that would be toxic to the subject. Explicit

disclosure of the use of a neuroprotective (and thus excitable tissue–protective) amount of erythropoietin "without a toxic increase in hemoglobin concentration or hematocrit" is provided in the specification at, *inter alia*, page 13, lines 16 through 29, and the working example in Section 8, page 31, line 13 to page 32, line 22. The specification makes clear that the dosage regimen of EPO is an amount sufficient to achieve a neuroprotective effect without a toxic increase in hematocrit as a consequence of the erythropoietic activity of EPO (*see, e.g.*, Specification at page 13, lines 17 through 29, and the working example in Section 8, page 31, line 6 to page 32, line 13).

Moreover, the specification makes abundantly clear that the dosages of EPO used for neuroprotection be *non-toxic* dosages of EPO. For example, all dosages prescribed are explicitly provided to be "effective non-toxic dosages of EPO" (page 4, lines 24 to 33, and again at page 23, lines 10-20). The specification enumerates the factors that should be considered to determine appropriate *non-toxic* dosage of erythropoietin, and specifies that the skilled practitioner is readily be able to make such a determination according to standard clinical techniques (*see*, *e.g.*, Specification at page 22, line 32 to page 23, line 9).

As an indication of the level of skill in the art at the time of the invention, the Examiner's attention is invited to the 2000 edition of the Physicians' Desk Reference ("PDR"), the art-accepted standard reference manual for practitioners at the relevant time; and, in particular, the section of the PDR relating to erythropoietin (see PDR, pp. 519-525 and 2125-2131, a copy of which is on record as Exhibit E of the Amendment under 37 C.F.R. § 1.111, dated February 26, 2003). The PDR shows that, depending on the patient population being treated with erythropoietin, different hematocrit ranges are targeted to avoid toxicity.[1] The PDR shows that practitioners monitor the patient's hematocrit during therapy with erythropoietin and, to avoid toxicity, adjust the dose and/or withhold treatment if the patient's hematocrit approaches or exceeds the upper limits of a target range.

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[1] For example, in patients with chronic renal failure, the PDR recommends dosing erythropoietin to achieve *non-toxic* target hematocrits ranging from 30% to 36% (*e.g.*, see PDR, p. 523, col. 1, *ll.* 17-96 and p. 2129, col. 1, *ll.* 8-93, and accompanying table in cols. 2 and 3). The PDR notes that toxicity in the form of polycythemia (a condition marked by an abnormal increase in the number of circulating red blood cells) can be avoided by carefully monitoring the hematocrit and adjusting doses of EPO, withholding erythropoietin if the hematocrit approaches the high-end of the target range (36% for this patient population) or increases by more than 4 points in any 2-week period, until the hematocrit returns to the suggested target range (30% to 36% for this patient population; see PDR, p. 523, col. 1, and p. 2129, col. 1, under "Dose Adjustment"). In contrast, for cancer patients on chemotherapy, the PDR teaches to adjust the dosage at a different hematocrit level, *i.e.*, if the hematocrit exceeds 40% (see p. 2129, col. 2, under "Dose Adjustment").

Therefore, the skilled practitioner would know how to control the hematocrit in any particular patient to avoid toxicity. As described above, this dosage may vary from subject to subject, depending on the condition of the patient and the surrounding circumstances. Such variation does not render the dosage unclear or ambiguous.

Thus, applicants believe the rejection under 35 U.S.C. § 112, second paragraph, for indefiniteness, is overcome and/or obviated by the present amendment and request its withdrawal.

CONCLUSION

Entry of the foregoing remarks and amendment into the record of the above-identified application is respectfully requested. Applicants estimate that the remarks and amendments made herein now place the pending claims in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Please charge any required fee to Jones Day Deposit Account No. 50-3013. A duplicate of this sheet is enclosed for accounting purposes.

Respectfully submitted,

Date: August 01, 2007

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Enclosures